Remarks

Reconsideration and withdrawal of the rejection of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 63, 65, 67-69, 71, 73, 75, 77-78, 80-81, and 83 are amended, and claims 66, 70 and 74 are canceled. Claims 63-65, 67-69, 71-73, and 75-83 are now pending in the application.

Amended claims 63, 71, 75, 78, and 81 are supported at page 98, lines 17-29, page 104, lines 9-12, page 105, lines 18-21, page 108, lines 21-27, and page 161, lines 4-16 of the specification.

Amended claims 65, 73, 77, 80, and 83 are supported by originally-filed claim 20.

Amended claims 67-69 are supported at page 98, lines 17-29, page 104, lines 9-12, page 105, lines 18-21, page 108, lines 21-27, page 161, lines 4-16, and the Example I in the specification.

The Examiner is thanked for the courtesies extended to Applicant's Representative and Dr. Grainger in the telephonic interview conduced on July 30, 2003 in which the outstanding rejection was discussed.

The Examiner rejected claims 63-83 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts that: 1) many of the diseases encompassed by the claims do not contain an inflammatory component; 2) the nexus between chemokine induced activity and all of the diseases encompassed by the claims has not been shown; 3) the *in vitro* assays disclosed in the specification are not representative of all the listed diseases; and 4) there is no evidence in the specification that the agents can prevent a disease. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

The claims, as amended, are generally directed to the use of chemokine peptides, substantially corresponding to sequences in the C-terminal half of a chemokine, and derivatives thereof, to prevent or inhibit hematopoietic cell, e.g., leukocyte, migration or recruitment. It is Applicant's position that the pending claims are more than adequately enabled. In this regard, in addition to the arguments previously presented in the present application with regard to

enablement, the Examiner is respectfully requested to consider the Rule 132 Declaration of Dr. David Grainger, one of the co-inventors of the present application, enclosed herewith.

In the Declaration, Dr. Grainger states that leukocyte (white blood cell) recruitment is a central component of the inflammatory process, both in physiological host defense and in a range of prevalent disorders with an inflammatory component (paragraph 4 of the Declaration). Dr. Grainger points out that chemokines are associated with the inflammatory response and are central regulators of leukocyte recruitment or migration (paragraph 4 of the Declaration). Dr. Grainger also states that molecules with anti-inflammatory activity are useful for the treatment of indications where inappropriate inflammation is a contributory factor to the pathogenesis and/or clinical symptoms of the indication, and that the present specification provides a list of exemplary indications in which inflammation plays a contributory role in the pathogenesis or clinical symptoms of those indications (paragraph 5 of the Declaration). Dr. Grainger then discusses four indications in detail, each of which has an inflammatory component (paragraphs 6-9 of the Declaration).

Dr. Grainger concludes that since chemokines are central regulators of leukocyte recruitment or migration, altering chemokine function affects leukocyte recruitment or migration dynamics and hence affects the progression of the disease state (paragraph 10 of the Declaration). Thus, once chemokines are implicated in a disease process, Dr. Grainger states that agents which have hematopoietic cell inhibitory activity are likely to be useful therapeutic modalities for indications in which leukocyte recruitment or migration contributes to pathogenesis or clinical symptoms (paragraph 10 of the Declaration).

Dr. Grainger also points out that there is substantial evidence that an agent of the invention can be employed prophylactically (paragraph 11 of the Declaration).

As further evidence that numerous other diseases have an inflammatory component, the Examiner is requested to consider the following documents (a copy of each document is enclosed herewith). For instance, Table 1 of Elson et al. (Gastroenterology, 109:1344 (1995)) summarizes components contributing to inflammatory bowel diseases, including regulatory T cells, T cell cytokines, B cells, neutrophils, mast cells and phagocytes. Karpus et al. (J. Immunol., 155:5003 (1995)) notes that experimental autoimmune encephalitis is a $CD4^+$ T cell mediated inflammatory disease that serves as a model for multiple sclerosis, and that the chemokine MIP-

1α plays a role in the pathogenesis of that disease. U.S. Patent No. 5,571,713 discloses that restenosis is often caused by a process in which monocytes and macrophage accumulate at areas of injury or inflammation, and may be treated by antisense MCP-1 oligonucleotides (column 1, lines 53-67 and column 2, lines 58-64). Ono et al. (Lab. Investig., 79:195 (1999)) relate that MCP-1 expression is upregulated after myocardial ischemia and that intravenous administration of anti-MCP-1 antibodies reduced infarct size and infiltration of macrophage (abstract). Similarly, MCP-1 is likely a molecular signal for the macrophage response to hypoxic-ischemia injury in the brain (see, for instance, Ivacko et al., J. Cerebral. Blood Flow Meta, 17:759 (1997)).

Leukocyte infiltration is also a feature of uveitis, and certain chemokines are upregulated in patients with idiopathic acute anterior ureitis (Verma et al., Curr. Eye Res., 16:1202 (1997)). Further, data presented in Marra et al. (Am. J. Path., 152:423 (1998)) support the position that MCP-1 secretion contributes to the formation and maintenance of the inflammatory infiltrate observed during chronic liver disease. In addition, pathogens including viruses, bacteria and fungi, are well-known to induce an inflammatory response.

Therefore, Applicant has provided more than sufficient evidence that many indications have an inflammatory component, and that there is a nexus between chemokine expression and indications having an inflammatory response. Thus, the *in vitro* assays disclosed in the specification, e.g., those which employ at least one chemokine and hematopoietic cells such as monocytes, are useful to identify agents that can prevent or inhibit hematopoietic cell recruitment or migration *in vivo*.

Further, as discussed in the Rule 132 Declaration enclosed herewith, the administration of agents of the invention can inhibit or substantially prevent an indication. In this regard, it is Applicant's position that it is well within the skill of the art worker to determine whether an individual is at risk of a particular indication. For example, risk factors for asthma (Businco et al., Ped. Pulm. Supple., 16:19 (1997)); psoriasis (Naldi et al., Br. J. Derma., 135:858 (1996)); nephritis (Jin et al., Nephron., 73:390 (1996)); atherosclerosis (Spence et al., Baillieres Clin. Neurol., 4:191 (1995)); Alzheimer's disease (Frecker et al., Can. J. Neurol. Sci., 21:112 (1994)); multiple sclerosis (Luchinetti et al., Neurology, 49:1413 (1997)); diabetes (Rewers et al., Diabetologia, 39:809 (1996)); and osteoporosis (Marone et al., Rev. Paul. Med., 115:1590

(1997)) are known (a copy of each document is enclosed herewith for the Examiner's convenience).

Thus, Applicant has enabled the claimed invention. Accordingly, withdrawal of the § 112(1) rejection is appropriate and is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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By their Representatives,

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Date September 25, 2003 By _____
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Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop AF, Commissioner of Patents, P.O.Box 1450, Alexandria, VA 22313-1450, on this 25 day of September, 2003

_____ _____
Name Signature